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A Comprehensive Review On Liposome-Based Drug Delivery: Their Method And Application

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Abstract: Liposomes are thought to be a promising and adaptable form of medication delivery. Site-targeting, sustained or controlled release, protection of pharmaceuticals from degradation and clearance, superior therapeutic effects, and fewer harmful side effects are some of the better qualities that liposomes have over conventional drug delivery systems. Due to these advantages, during the past few decades, a number of liposomal medicinal formulations have been approved and used in clinical settings. Spherical-shaped lipoidal vesicles known as liposomes are being studied extensively as medication carriers to increase the delivery and bioavailability of medicinal substances. Liposomes are also known as targeted drug delivery systems because they are a very effective way to deliver an active medication to a specific area of the body without damaging or trapping other areas. Liposomes come in a variety of sizes and can be used to treat a wide range of conditions. They work as a vehicle to deliver a medication or substance to the active site at a specific rate and time without damaging other body parts. Liposomes are stable and biocompatible. Their ability to trap hydrophilic and lipophilic drugs (of amphipathic type) in their compartment and produce a controlled-release action is a unique characteristic.

Index Terms **–** Liposomes, Liposomal drug delivery, Targeted drug delivery, Controlled release

I. INTRODUCTION

The Greek words "Lipos" which means "fat," and "Soma," which means "body," were combined to make liposomes, which are spherical concentric vesicles.[1] When compared to traditional medications, the main goal of targeted drug delivery is to effectively transport a medication straight to the site of action in order to increase efficacy and decrease side effects. [2] Liposomes have attracted a lot of attention among other carrier systems because of their adaptability. Liposomes' versatile physicochemical and biophysical properties make them an appealing delivery system since they may be easily modified to satisfy a range of delivery requirements.[3] Liposomes are self-assembled drug vesicles based on phospholipids that enclose a core aqueous compartment in a concentric series of numerous bilayers (multilamellar) or a single bilayer (uni-lamellar).[4] The phospholipid bilayer of liposomes is 4–5 nm thick, and their sizes range from 30 nm to the micrometre scale.[5] Amphiphilic phospholipids have a hydrophilic polar head and a hydrophobic hydrocarbon tail.[6]Alec Bangham and his coworkers at Babraham Cambridge in the UK started the study of liposomology in the mid-1960s. They reported the structure of liposomes for the first time in 1964.[7,8] A major advancement in the field of drug delivery systems was made with the discovery of liposomes.[9] Liposomes are beneficial because they have potential medicinal or other uses and serve as carriers for a range of medications. Liposomal drug delivery is becoming more popular because of its benefits in a number of fields, including biological, cosmetic, and drug delivery.[10]Liposomes are good drug transporters because they protect the encapsulated chemicals from physiological degradation, prolong the drug's half-life, regulate the release of drug molecules, and have great biocompatibility and safety.[11,12] Liposomes can encapsulate both hydrophilic and hydrophobic molecules on a single platform because they are mostly made of biocompatible and biodegradable materials.[13]

II. Fundamentals of liposomes

Liposomes are small vesicles made up of an aqueous core surrounded by one or more lipid bilayers. They are biocompatible and biodegradable because of their structure, which is similar to that of biological membranes[14]. Because of their special structure, liposomes can contain both hydrophilic and hydrophobic medications; the hydrophilic ones stay in the aqueous core, while the hydrophobic ones are injected into the lipid bilayers.[15]

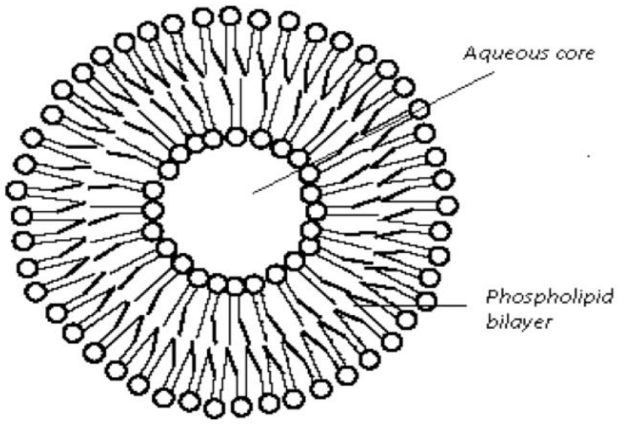

Figure 1: Design of liposome

Depending on their composition and manner of manufacture, liposomes can range in size from 20 nm to several micrometres. Drug distribution to various tissues and cellular compartments can be customized thanks to this size versatility.[16]Liposomes are superior medication transporters due to a number of important characteristics:

1. Biocompatibility: Liposomes are often non-toxic and well-tolerated by the body due to their natural or synthetic lipid composition.[17]

2. Versatility: They have the ability to encapsulate a broad variety of medicinal substances, including macromolecules like proteins and nucleic acids as well as tiny compounds.[18]

3.Cargo protection: Liposomes protect the medications they encapsulate against deterioration and early elimination, which may enhance the pharmacokinetic profile of the medication.[19]

4.Targeted delivery: To increase the specificity of liposomes for particular tissues or cell types, targeted ligands can be added to their surface.[20]

5.Controlled release: By adjusting the lipid composition and environmental responsiveness, medications can be released from liposomes in a controlled manner.[21]

III. Structural components of liposomes: -

Phospholipids:

The main structural elements of liposomes are phospholipids, which create the bilayer that surrounds the aqueous core. These amphiphilic molecules consist of a hydrophilic head group and two hydrophobic fatty acid tails.[22] When synthesizing liposomes, the following phospholipids are most frequently used:

- **Phosphatidylcholine (PC):** The most widely utilized phospholipid because of its stability and biocompatibility, PC can be manufactured or obtained naturally from sources like eggs or soy.[23]
- **Phosphatidylethanolamine (PE):** PE can improve the fusion of liposomes with cell membranes and is frequently employed in conjunction with PC.[24]
- **Phosphatidylserine (PS):** Anionic liposomes, which interact differently with different cell types, can be made using negatively charged PS.[25]
- The negatively charged phospholipids phosphatidylglycerol (PG) and phosphatidylinositol (PI) are employed to adjust the liposomes' surface charge.[26]

The stability, size, charge, and drug release characteristics of the liposome are all greatly influenced by the phospholipid selection. Unsaturated phospholipids, such as dioleoyl phosphatidylcholine, produce more fluid and permeable membranes, whereas saturated phospholipids with long acyl chains, such as dipalmitoyl phosphatidylcholine, generate more stiff and stable bilayers.[27]

Cholesterol:

A key ingredient in many liposomal compositions, cholesterol is essential for regulating membrane characteristics.

- **Membrane fluidity:** A more stable membrane across a wider temperature range results from cholesterol's reduction of the lipid bilayer's fluidity above the phase transition temperature and its enhancement below it.[28]

• **Permeability:** Cholesterol reduces membrane permeability by bridging the spaces between phospholipid molecules, which lessens medication leakage.[29]

• **Stability:** Cholesterol improves liposome stability in biological fluids by strengthening the lipid bilayer's mechanical integrity.[30]

• **Phase transition:** It removes phospholipids' abrupt phase transition, which may help preserve the integrity of liposomes during administration and storage.[31]

Depending on the desired liposome characteristics and the medicine being encapsulated, the molar ratio of cholesterol to phospholipids normally falls between 1:4 and 1:1.[32]

IV. Classification of liposomes:

The Liposomes classification is based on
i. Structure
ii. Preparation Process
iii. Constituent and its Application

1) Based on structure:

Table 1: Diameter Size and number of lipid layers of different vesicles

Sr.No	Vesicle type	Abbreviation	Diameter Size	No. of Lipid Layers
1.	Unilamellar vesicle	UV	All size ranges	One
2.	Small Unilamellar vesicle	SUV	20-100 nm	One
3.	Medium Unilamellar vesicle	MUV	More than 100 nm	One
4.	Large Unilamellar vesicle	LUV	More than 100 nm	One
5.	Giant Unilamellar vesicle	GUV	More than 1.0 µm	One
6.	Oligolamellar vesicle	OLV	0.1-1.0 µm	Approx 0.5
7.	Multilamellar vesicle	MLV	More than 0.5 µm	5-25
8.	Multi vesicular vesicle	MV	More than 1.0 µm	Multi compartmental structure

2) Based on Method of Preparation:

Table 2: Different methods of preparation and the vesicles developed by those methods

Sr.No	Preparation Method	Vesicle Type
1.	Lamellar vesicle of a single or oligo formed by reverse phase evaporation	REV
2.	Multi lamellar vesicles formed by the method of reverse phase evaporation	MLV-REV
3.	Stable pluri lamellar vesicle	SPLV
4.	Frozen and thawed multi lamellar vesicle	FATMLV
5.	Vesicle prepared by extrusion technique	VET
6.	Dehydration-Rehydration method	DRV

3) Based on Composition and Application:

Table 3: Different Liposome with their Compositions

Sr.No	Type of Liposome	Abbreviation	Composition
1.	Conventional	CL	Neutral or negatively charge phospholipids and cholesterol
2.	Fusogenic	RSVE	Reconstituted Sendai virus envelops
3.	pH sensitive	-	Phospholipids such as DOPE or PER with either OA or CHEMS
4.	Cationic	-	Cationic lipid with DOPE
5.	Long circulatory	LCL	Neutral high temp, cholesterol, and 5-10% PEG, DSP
6.	Immuno	IL	CL or LCL with monoclonal antibody linked or sequences of recognition

V. METHODS OF PREPARATION:

Basically, all the liposome preparation strategies have four basic steps.
I. Drying down lipid from organic solvent
II. Dispersing the lipid in aqueous media
III. The purification of the resulting liposome
IV. Examination of final products

There are different methods involved in the preparation of liposomes

1) Passive loading technique

During the liposome synthesis process, medications are encapsulated using passive loading procedures. Lipids are dissolved in an organic solvent, dried to create a thin film, and then hydrated with an aqueous medication solution in the straightforward thin-film hydration procedure. Despite being simple, this approach frequently yields low encapsulation efficiency for medications that are hydrophilic.[36] For hydrophilic medications, the reverse-phase evaporation approach provides a better encapsulation efficiency. This method involves creating a water-in-oil emulsion with lipids and the aqueous drug solution, then vacuum-removing the organic solvent.[37]

The freeze-thaw technique enhances the encapsulation of macromolecules by quickly freezing and thawing MLVs holding the medication. To increase overall efficiency, this strategy is frequently integrated with other approaches.[38] Sonication uses soundwaves to disrupt MLVs into SUVs, producing small, homogeneous liposomes. However, this method carries the risk of drug degradation due to heat generation.[39] Extrusion is a technique that forces liposomes through polycarbonate membranes to produce uniform-sized liposomes while maintaining the integrity of sensitive compounds.[40]

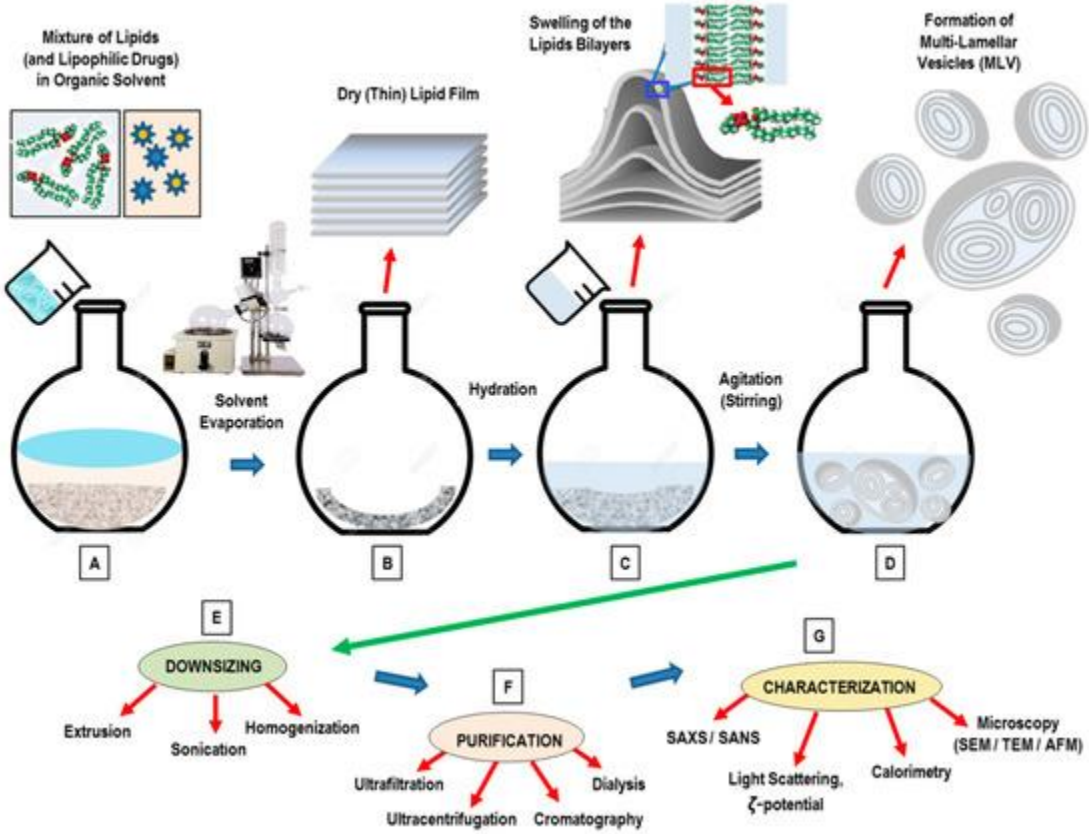

Figure 2: Lipid film hydration method

2)Active loading techniques

Using active loading techniques, a gradient is created to promote drug encapsulation following liposome synthesis. The pH gradient approach works well with weak bases or acids because it produces a pH differential between the liposome's outside and interior. For certain medications, this technique can achieve high encapsulation efficiency, frequently above 90%.[41] The ammonium sulfate gradient approach loads amphipathic weak bases using an ammonium sulfate gradient. It offers consistent drug retention and is very effective for medications like doxorubicin.[42] Ion gradients, such calcium acetate, are used for loading in the ion gradient method. Drugs that generate insoluble calcium complexes benefit greatly from this method, which offers increased stability and high loading efficiency.[43]

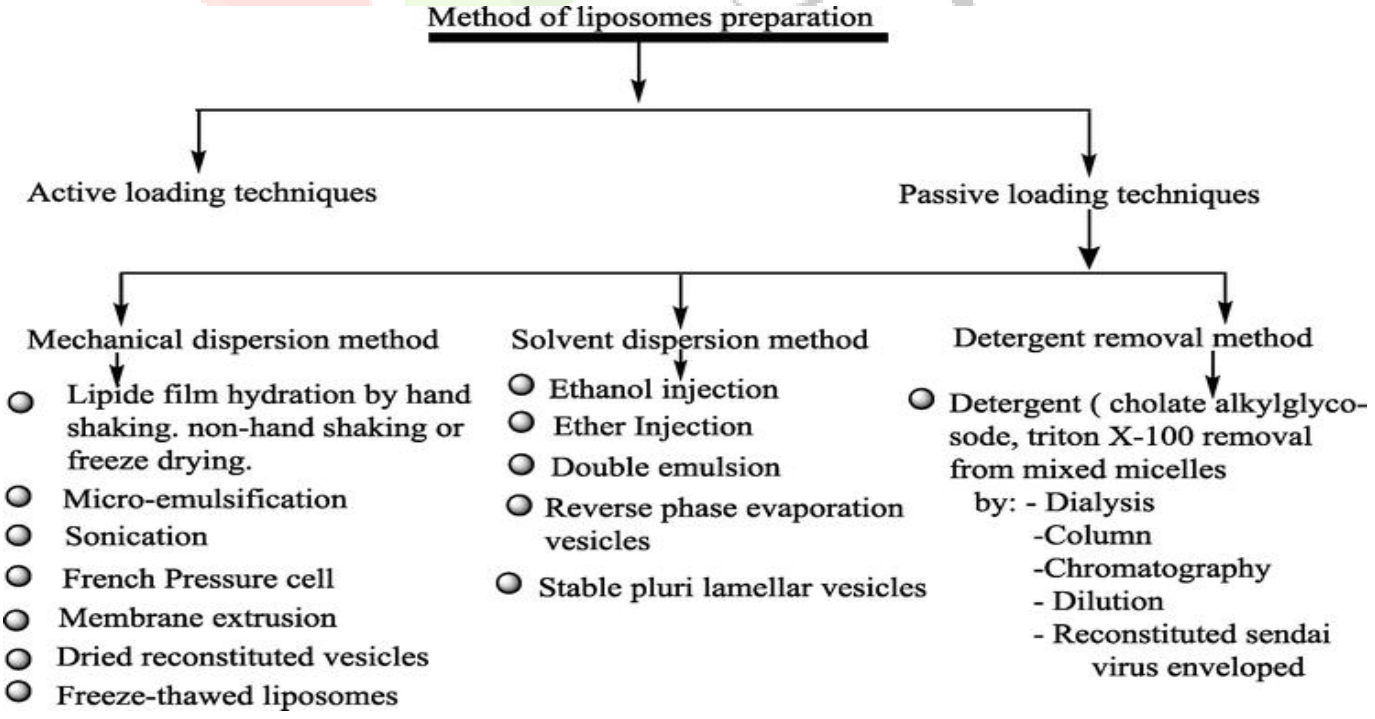

Figure 3: Methods of liposome preparation

VI. LIPOSOMES STABILITY:

The stability of the liposomes during the production, storage, and delivery processes is used to evaluate a drug molecule's therapeutic efficacy. Throughout development and storage, a stable liposome formulation needs to maintain the active molecule's chemical and physical integrity. A stability study includes evaluating the product's microbiological, chemical, and physical characteristics as well as ensuring the product's integrity throughout storage.[44]

Physical stability:

Drug leakage from vesicles during storage may cause the fusion and shattering. This could make the liposomal medicinal product less physically stable. Consequently, the vesicles' size distribution and morphology are crucial factors in determining their physical stability.[45] Light scattering and electron microscopy are employed to determine the vesicles' visual appearance (morphology and size). Although cholesterol makes lipid membranes stiffer, its content in liposomes should not exceed 50%. It is essential for the bioactive molecule's stability and survival within the liposome. Avoiding excessive unsaturation in the phospholipids, regulating pH levels, and storing at 4°C without freezing or light exposure are ways to preserve physical stability.[46]

Chemical stability:

Chemically, unsaturated fatty acids, such as phospholipids, are susceptible to oxidation and hydrolysis, which could alter the medicinal product's stability. A liposomal formulation's stability is largely dependent on the solvent system, buffered species, pH, and ionic strength. Because free radicals are produced during the oxidation process, cyclic peroxides and hydroxy-peroxidases are formed as a result of oxidation deterioration. Protecting liposomes from light, adding antioxidants such α-tocopherol or butylated hydroxyl toluene (BHT), creating the product in an inert environment (such as one that contains nitrogen or argon), or adding EDTA to eliminate trace heavy metals are all ways to stop oxidative deterioration.[47]The hydrolysis of the ester bond at the C-4 position of the glycerol moiety of phospholipids results in the formation of lyso-phosphatidylcholine. The liposomal contents' permeability will rise as a result. Therefore, it becomes crucial to regulate the lyso-phosphatidylcholine limit in the lysosome pharmacological product. The creation of lyso-phosphatidylcholine free liposomes using phosphatidylcholine can attain this goal.[48]

VII. MECHANISM ACTION OF LIPOSOME:[49]

An area of aqueous solution enclosed by a hydrophobic membrane makes up a liposome. Liposomes can transport both hydrophilic and hydrophobic molecules because hydrophobic compounds dissolve readily in lipid membranes. The drug's physiochemical properties and lipid makeup will determine how far it can be found. Lipid bilayers combine with other cell bilayers (the cell membrane) to release the liposomal content, which allows the release of essential therapeutic molecules to the site of action.

The steps involved in medication delivery via liposomes are as follows:

1. The adsorption of liposomes results in their interaction with the cell membrane.
2. Liposome adsorption on the cell membrane, followed by internalization into the liposomes and engulfment (endocytosis).
3. Direct delivery of liposomal contents in the cytoplasm is achieved via lateral diffusion and lipid mixing, which fuse the lipid bilayers of liposomes with the lipoidal cell membrane.
4. Lipid transfer proteins in the cell membrane may readily identify liposomes and initiate lipid exchange because the phospholipids in the cell membrane and the lipid membrane of liposomes are identical.

VIII. Applications of Liposomal Drug Delivery Systems:

Cancer therapy:

Numerous formulations of liposomal drug delivery systems have been licensed for clinical use, demonstrating their widespread use in cancer therapy. The most well-known example is DoxilÆ, a PEGylated liposomal version of doxorubicin that has demonstrated less cardiotoxicity and increased efficacy in a variety of cancer types as compared to free doxorubicin.[50]Other anticancer medications like cisplatin, irinotecan, and paclitaxel have also shown improved therapeutic indices in liposomal form. Liposomal drug delivery has several benefits for cancer treatment, such as better pharmacokinetics, increased tumor accumulation through the EPR effect, and decreased systemic toxicity. Recent advancements in this area include the creation of liposomal formulations for combination therapy and multifunctional liposomes that combine drug delivery with imaging capabilities (theragnostic).[51]

Gene therapy:

Liposomes have demonstrated great promise as non-viral gene therapy vectors, especially cationic liposomes. These methods facilitate cellular absorption and endosomal escape while efficiently condensing and protecting nucleic acids (DNA, RNA, and siRNA) from degradation.[52] Numerous genetic abnormalities, malignancies, and infectious diseases have been studied using liposomal gene delivery techniques. The creation of pH-sensitive and targeting liposomes to improve the effectiveness and specificity of gene transfection is one recent discovery in this area. Particular emphasis has been paid to the use of liposomes for mRNA delivery, particularly in the context of vaccine development.[53]

Vaccine delivery:

Liposomes have shown great promise as vaccine delivery vehicles because they can improve antigen presentation, increase antigen stability, and alter immune responses. Liposomal vaccines can be made to target certain immune cells and can contain a variety of antigens, including proteins, peptides, and nucleic acids.[54] The co-delivery of antigens and immunostimulatory molecules is made possible by the versatility of liposomal systems, which may improve the effectiveness of vaccines. The liposomal adjuvant systems included in approved influenza and hepatitis A vaccinations are notable examples. The potential of this approach for quick vaccine production has been further demonstrated by the recent success of liposome-based mRNA vaccines for COVID-19.[55]

Diagnostic imaging:

Liposomes have been used as contrast agents for a variety of imaging modalities in diagnostic imaging. Gadolinium or manganese-containing paramagnetic liposomes have been created as magnetic resonance imaging (MRI) contrast agents. By enhancing contrast in particular tissues or organs, these methods may help with disease characterization and detection.[56]

Nuclear imaging methods including single-photon emission computed tomography (SPECT) and positron emission tomography (PET) have been studied using radiolabeled liposomes. These methods can help with the development and improvement of liposomal drug delivery systems by offering data on target site accumulation and liposome biodistribution.[57] The idea of theranomic liposomes, which combine medicinal and diagnostic properties, has drawn a lot of attention. These multipurpose systems make it possible to track medication administration and therapy response in real time, which may lead to the development of individualized treatment plans.[58]

IX. Marketed formulations of Liposomes:[59]

Table 4: marketed formulations of liposomes

Sr.No	Product	Drug	Company
1.	AmbisomeTM	Amphotericin B	Nexstar pharmaceuticals Inc., CO
2.	AbelcetTM	Amphotericin B	The Liposome Company, NJ
3.	AmphocilTM	Amphotericin B	Sequus pharmaceuticals, Inc., C. A
4.	DoxilTM	Doxorubicin	Sequus pharmaceuticals, Inc., C. A
5.	DaunoXomeTM	Daunorubicin	Nexstar pharmaceuticals, Inc., CO
6.	MiKasomeTM	Amikacin	Nexstar pharmaceuticals, Inc., CO
7.	DC99TM	Doxorubicin	Liposome CO., NJ, USA
8.	EpaxelTM	Hepatitis A Vaccine	Swiss Serum Institute, Switzerland
9.	ELA-MaxTM	Lidocaine	Biozone Labs, CA, USA

X. ADVANCEMENTS IN LIPOSOMES:

Ethosomes: They work well to deliver 30% ethanol and soy phosphatidylcholine to the skin.

immuno liposomes: Antibodies were used to modify immuno liposomes.

Niosomes: These are tiny unilamellar vesicles made of non-ionic surfactants.[60]

Stealth liposomes: are novel liposome varieties intended to improve stability and prolong their half-life in circulation. Polyethylene glycol (PEG) should be used to coat the liposomes in order to prepare them.[61]

XI. CONCLUSION: -

Liposomes are a novel and promising drug delivery method with a broad range of uses in the pharmaceutical industry. Numerous studies conducted over the years have shown their ability to address a number of issues related to conventional medication delivery techniques. A potential type of drug delivery methods, liposomes have a number of benefits for improving the safety and therapeutic efficacy of different medications. With a wide range of applications in the pharmaceutical sector, liposomes are a new and promising drug delivery

technology. Several research over the years have demonstrated their capacity to tackle various problems associated with traditional drug delivery methods. Liposomes are a promising class of drug delivery vehicles that offer several advantages for enhancing the therapeutic effectiveness and safety of various drugs.

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